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Brief Clinical Report

Mild "Duplication 6q Syndrome": A Case With Partial Trisomy (6)(q23.3q25.3)

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We report on a female infant with partial 6q trisomy (46,XX,dir dup(6)(q23.3q25.3)) and phenotypic characteristics of the "duplication 6q syndrome," including intrauterine growth retardation, dolichocephaly, depressed nasal bridge, almond-shaped palpebral fissures, short neck, flexion-contractures of the wrists, and mild generalized hypertonia. Although clearly belonging to the described "duplication 6q syndrome," her features were milder than those found in the literature. Comparison of the phenotype of this child with other published reports indicates that specific phenotypic components of the duplication 6q syndrome cannot be attributed to duplication of a specific band or bands on 6q. Am. J. Med. Genet. 68:450–454, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: duplication 6q syndrome; growth retardation; chromosome 6; flexion contractures

INTRODUCTION

Since first proposed [Breuning et al., 1977], the duplication 6q syndrome has been documented repeatedly and can be recognized as a distinct entity [Tipton et al., 1979; Dallapiccola et al., 1978; Uhrich et al., 1991; Turleau and de Grouchy, 1981; Pivnick et al., 1990]. The phenotype comprises severe physical and mental retardation, feeding difficulties, microcephaly, prominent forehead, downward slanting palpebral fissures, flat nasal bridge and facial profile, "carp mouth," micrognathia, short webbed neck, flexion deformities, club feet, and abnormal palmer creases. Of the 25–30 reported cases, most were the result of abnormal segregation of a balanced translocation carried by a parent. Very few patients had a "pure" 6q duplication [Turleau and de Grouchy, 1981; Ohta et al., 1993; Giardino et al., 1994]. We have tried to compare the phenotypic characteristics of our patient with those in other published reports in an attempt to better define limited regions on 6q responsible for the particular traits that make up the "duplication 6q syndrome."

CLINICAL REPORT

The proposita, R.P. (Fam 30054, Fig. 1, 2), is a 2-month-old black girl, the fourth child of a 25-year-old woman and a 41-year-old father. One sib and two halfsibs are normal. The pregnancy was uncomplicated. However, the mother reported that although the intrauterine movements began around 5 months gestation, the child was less active than previous children. R.P. was born at 39 weeks by cesarean section due to fetal distress. Apgar scores were 8 (at 1 minute) and 9 (at 5 minutes). Growth parameters at birth were below normal: weight 2,080 g (<5th percentile), length 47 cm (10th percentile), and head circumference (OFC) 31.0 cm (<5th percentile). At birth, the infant was noted to have dolichocephaly, large anterior and posterior fontanelles with open sutures, prominent occiput, broad nasal bridge, epicanthal folds, long fingers, bilateral single palmar creases, flexion-contractures of the wrists, dorsiflexion of the first toes, and generalized hypotonia. Results of a head CT scan and an ophthalmological exam were normal. An ECG showed sinus bradycardia. The echocardiogram demonstrated mild tricuspid insufficiency, a small PDA (patent ductus arteriosus), and small ASD (atrial septal defect). A chest roentgenogram showed moderate cardiomegaly.

At age 2 months, all growth parameters were normal for age. Weight was 4,330 g (25th centile); length was 55.4 cm (35th centile), and OFC was 37.8 (50th centile). The main physical findings (Fig. 1, 2) were dolichocephaly with prominent occiput, prominent forehead, large anterior fontanelle, fingertip posterior fontanelle, open metopic suture, horizontal almond-shaped palpebral fissures, infraorbital creases, blue-tinted sclerae, and hypertelorism (ICD 80th percentile and OCD 60th percentile). The ears were normal

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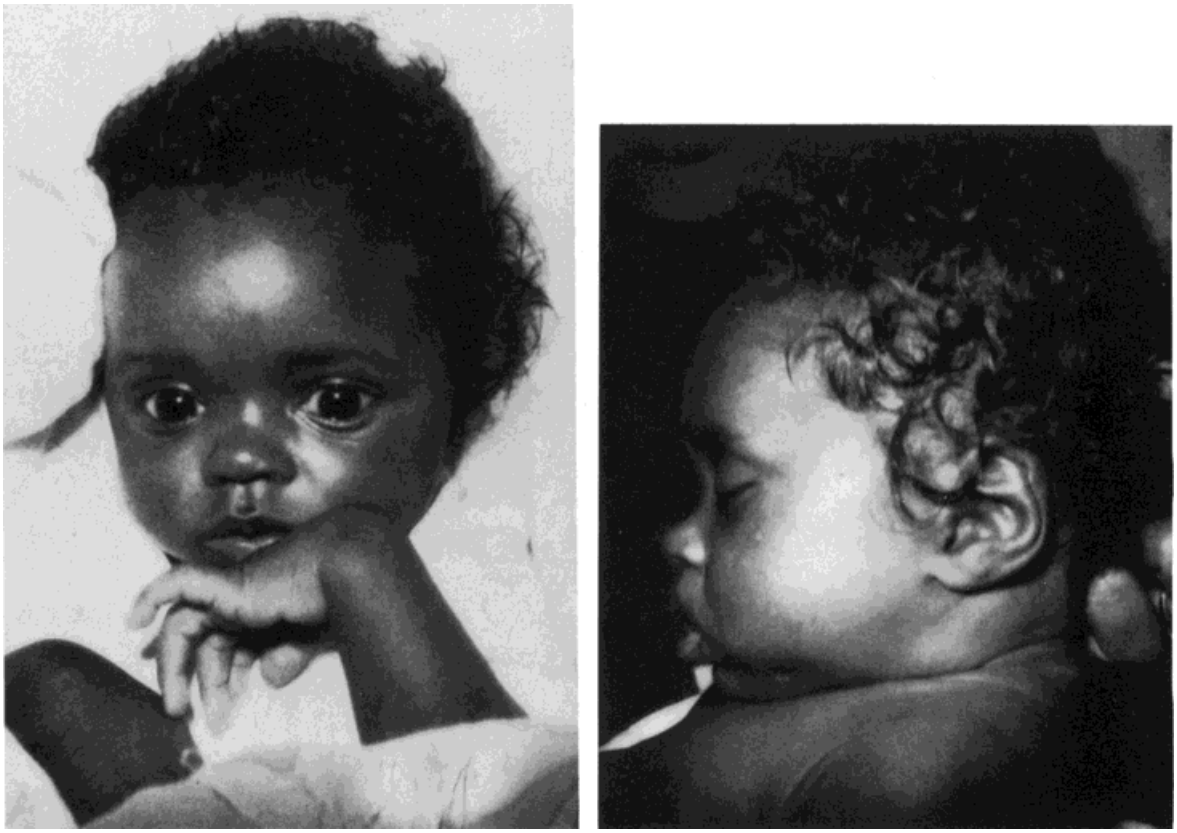

Figs. 1 and 2. Patient at age of 2 months.

in length and slightly posteriorly angulated. She had a broad, depressed nasal bridge, short philtrum, midface hypoplasia, and "carp mouth." The neck was short but not webbed. She had a grade 3/6 systolic murmur, 90° flexion contractures at the wrists, long fingers, dorsiflexion of the first toes, mild syndactyly of toes 2–3, an umbilical hernia, and mild generalized hypertonia.

MATERIALS AND METHODS

Peripheral blood was collected from the proposita and her mother; we were unable to obtain a paternal blood sample. Peripheral blood cultures for cytogenetic analysis were processed using standard laboratory procedures. Metaphases were analysed at the 575 to 620 band level.

For FISH analysis, a biotinylated whole-chromosome 6 paint probe (Vysis) was hybridized to metaphase spreads and detected with avidin-FITC according to the manufacturer's protocol. Images were analysed on a Leitz Aristoplan microscope, using a standard triple bandpass filter.

RESULTS

The patient had a chromosomal abnormality, consisting of a small duplication of the long arm of chromosome 6 (Fig. 3). Her karyotype was 46,XX,dir dup(6)(q23.3q25.3). The karyotype of the mother was normal. FISH analysis with the chromosome 6 specific paint probe (Vysis) showed that the extra material on the patient's abnormal chromosome 6 was of 6 origin (Fig. 4), thus confirming the G-banding results.

DISCUSSION

The findings in this child fit those of the duplication 6q syndrome [Turleau and de Grouchy, 1981; Ohta et al., 1993; Giardino et al., 1994]. However, when compared with other cases, her manifestations are somewhat milder. At 2 months, her growth was normal. Only one other patient with an identical karyotype has been reported [Ohta et al., 1993], but phenotype was not described. Our case differs from many reported cases in whom the karyotypes demonstrated duplications and deletions resulting from abnormal segregation of parental balanced translocations [Turleau and de Grouchy, 1981; Clark et al., 1980; Chase et al. 1983; Franchino et al., 1987; Neu et al., 1981; Schmid et al., 1979; Robertson et al., 1975; Chen et al., 1976; Taysi et al., 1983; Stamberg et al., 1981]. Therefore, the phenotypes could be the result of not only the 6q duplications but also of the associated deletions. The autosomal arms involved were 2q, 3p, 4q, 5q, 10q, 11q, 14q, 15p, 15q, 16q, 18q, 21p, and 22p. Very few cases were de novo duplications [Ohta et al., 1993; Giardino et al., 1994].

It has been suggested that most of the patients with duplication 6q syndrome have a duplication of band

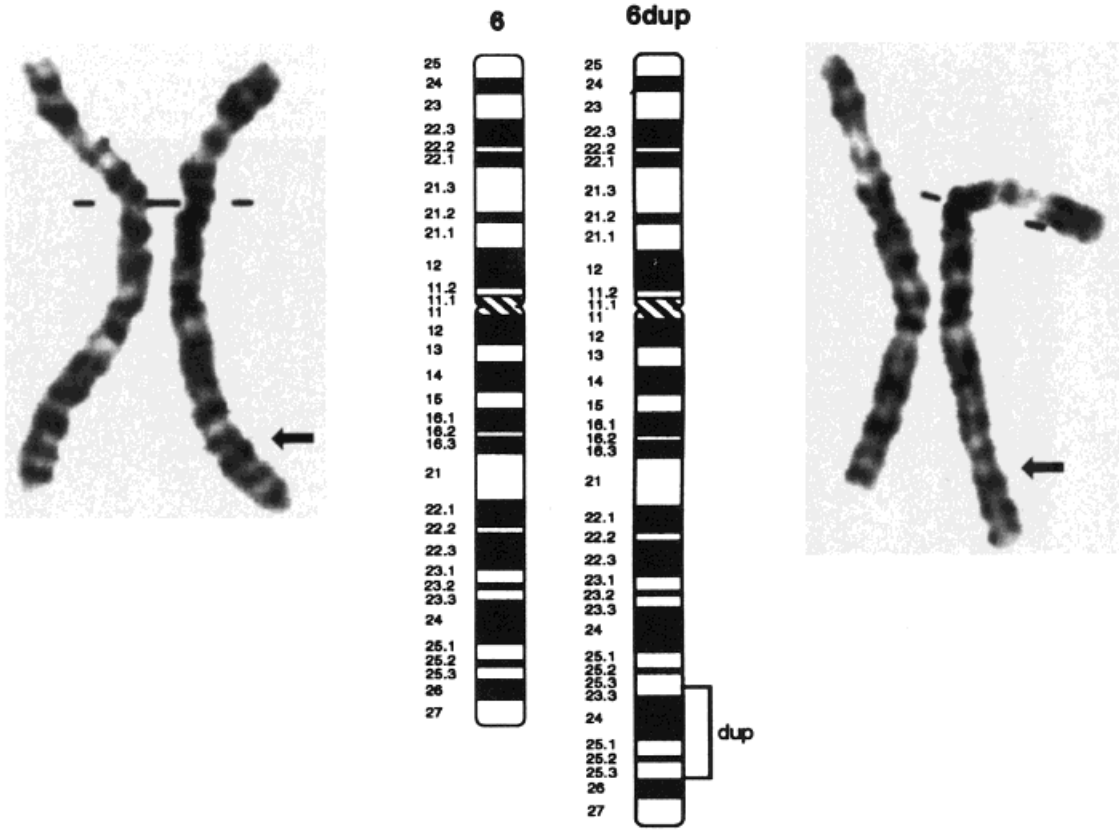

Fig. 3. Examples of the duplicated 6q23.3-25.3 of the proposita. The arrows indicate the duplicated chromosomes.

Fig. 4. Results of the FISH analysis on a metaphase spread from the proposita with a chromosome 6 specific painting probe. There is uniform hybridization on both the normal and abnormal (arrow) chromosomes 6.

6q26 and that this region is critical for phenotype expression [Turleau and de Grouchy, 1981]. Given the milder clinical presentation of our case and the fact that this patient had a small duplicated segment, we compared our data with published data in an attempt to assign various component traits of the "duplication 6q syndrome" to specific regions on 6q, or to find or confirm a critical region responsible for some of the constant signs (Table I). Included in this effort were only cases with "pure" 6q duplications [Schroer et al., 1980; Turleau and de Grouchy, 1981; Brøndum-Nielsen et al., 1993; Ohta et al. 1993; Giardino et al., 1994], without associated aberrations of another chromosome in the karyotype or cases in which the additional 6q material was translocated onto the short arm of an acrocentric chromosome [Pivnick et al., 1990; Taysi et al., 1983; Stamberg et al., 1981] or inserted into another autosome [Chen et al., 1976; Pierpont et al., 1986]. Table I shows that findings of the syndrome appeared in all of the patients described, not only in those with duplication of 6q26. Our patient, with a duplication of 6q23.3 to 6q25.3 had many of the consistent features of the syndrome, although less severely affected overall. As the proband does not have a duplication of 6q26, this band is unlikely to be the critical region for the syndrome. It is more likely that genes from different regions of 6q interact and influence phenotypic traits so

TABLE I. Summary of Cases With "Pure" Partial Trisomy of 6q

Phenotype	Pierpont Trisomy 6q13-q21	Chen (2 cases) Trisomy 6q13-q22		Stamberg Trisomy 6q21-qter	Taysi Trisomy 6q22-qter	Pivnik Trisomy 6q23-qter	Schroer Trisomy 6q25-qter	Brøndum-N Trisomy 6q26-q27	Turleau Trisomy 6q26-qter	Present case Trisomy 6q23.3-25.3
Mental retardation	+	+	+	n.a.	+	n.a.	+	+	+	Not known
Prenatal gr. retardation	−	−	−	n.a.	+	+	+	+	−	+
Postnatal gr. retardation	+	+	+	n.a.	+	+	+	+	+	−
Microcephaly	−	+	+	+	+	+	+	−	+	+ (At birth)
Acrocephaly	−	−	−	−	−	+	+	−	−	−
Prominent forehead	+	−	−	−	+	−	+	+	+	+
Downslanting p.f.	+	+	+	n.a.	+	+	+	+	−	−
Hypertelorism	+	+	+	+	+	+	+	+	−	+
Flat/ broad nasal bridge	+	+	+	n.a.	+	−	+	+	−	−/+
"Carp" mouth	+	−	−	n.a.	+	+	+	+	+	+
Micrognathia	−	+	+	n.a.	+	+	+	+	+	+
Low set/rotated ears	−/+	−	−	+	+/+	−	−	n.a.	−	+
Short/ webbed neck	−		n.a.[a]	−/+	+	+	+	+	+	+/−
Joint contractures	+	−	+	+	+	+	+	+	+	+
Clinodactyly	+	+	+	−	+	−	−	+	−	+
Syndactyly	+	−	−	−	−	−	+	+	−	+
Talipes equinovarus	+	−	−	+	+	+	+	−	−	−
Cardiac murmur/anomaly	+	−	−	+	+	+	+	−	−	+
Genitourinary anomaly	+	−	−	+	+	+	−	+	+	−
Cerebral anomaly	−	−	−	+	−	−	−	−	−	−
Other defects	Cleft palate Retinal detachment	− Arched palate −	Scoliosis Seizures	Omphalocele Arched palate	Brachycephaly Choanal stenosis	−	Blue sclerae	Glaucoma Hypoglycemia Hypothyroid Seizures	Hypospadias	Blue sclerae Umbilical hernia

[a] n.a. = not available.

that over-representation of various bands may modulate gene expression and determine similar outcomes [Wilson, 1990]. Alternatively, as standard cytogenetic analysis has limited resolution, it is possible that there is a small region of overlap between the duplicated region in our proposita and the critical region (6q26) described before, and that gene(s) in this limited region are responsible for the phenotype. Molecular analyses with locus-specific DNA probes for this region would resolve these questions.

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